

R E M A R K S

Presently Claimed Invention

The present claims are directed to a method for detecting colon cancer wherein the tumor marker is COX-2. The method comprises: a) homogenizing collected feces in the presence of an Rnase inhibitor to prepare a suspension thereof, without separating cell components from the feces; b) extracting RNA from the suspension from step a) to provide extracted RNA; c) carrying out reverse transcription on the extracted RNA from step b) to provide cDNA; d) amplifying the cDNA from step c) and e) detecting the amplified COX-2 from step d) (see applicants' claim 5).

Obviousness Rejections Under 35 USC 103

1. The previous rejection of claims 20 and 23 under 35 USC 103 as being unpatentable over Alexander and Raicht (1998), Digestive Diseases and Sciences, Vol. 43, No. 12, pp. 2652-2658, as evidenced by Ultraspec™-II RNA, Isolation System, Biotechx

Bulletin, No. 28, 1993, in view of Sano et al., (1995), Cancer Research, 55: 3785-3789 was maintained for the reasons set forth in item no. 4 on pages 2 to 4 of the November 26, 2008 Office Action.

2. Claims 5, 17 to 18, 20 and 22 to 23 were rejected under 35 USC 103 as being unpatentable over Alexander and Raicht, (1998), Digestive Diseases and Sciences, Vol. 43, No. 12, pp. 2652-2658, as evidenced by Ultraspec™-II RNA, Isolation System, Biotechx Bulletin, No. 28, 1993, in view of Sano et al., (1995), Cancer Research, 55: 3785-3789 for the reasons set forth in item no. 7 beginning at the middle of page 4 and continuing to the bottom of page 7 of the November 26, 2008 Office Action.

It was admitted in the November 26, 2008 Office Action that regarding claim 5, Alexander and Raicht do not teach the use of the marker COX-2 as a marker suitable for colon cancer detection.

3. Claims 15 and 16 were rejected under 35 USC 103 as being unpatentable over Alexander and Raicht and Sano et al. in view of Godfrey et al. (USP 7,101,663) for the reasons stated in item no. 8 on pages 8 to 9 of the November 26, 2008 Office Action.

It was admitted in the November 26, 2008 Office Action that Alexander and Raicht; and Sano et al. do not teach wherein in step (e) amplifying the cDNA from step d) is carried out by a nested PCR.

Applicant's Reply to the Obviousness Rejections

A. The position was taken at the top of page 4 of the November 26, 2008 Office Action that since the sample set is small, the data of record did not show any unexpected improvement for the detection of colon cancer using occult blood.

In reply to the above contention, submitted concomitantly herewith is a DECLARATION UNDER 37 CFR 1.132 of Shigeru KANAOKA dated April 23, 2009, which provides additional comparative data.

The enclosed April 23, 2009 KANAOKA DECLARATION provides comparative test data using an increased number of cases (from 30 to 70 patients with colorectal cancer (CRC) and from 22 to 34 control subjects). It is respectfully submitted that the results set forth in the April 23, 2009 KANAOKA DECLARATION demonstrate that the studies population which consisted of 70 patients with

CRC and 34 control subjects were enough to judge the effectiveness of the methods. See (2)(a) Comparison of COX-2 assay between CEA assay and fecal occult blood test), the results for which we reproduced as follows.

Comparison of COX-2 Assay Between CEA Assay
and Fecal Occult Blood Test

<u>marker</u>	<u>sensitivity</u>	<u>specificity</u>
COX-2	85.7% (60/70)	100.0% (34/34)
CEA	92.9% (65/70)	11.8% (4/34)
occult blood	73.5% (50/68)	82.4% (28/34)

B. The position was taken at the top of page 4 in the November 26, 2008 Office Action that CEA was not shown to be a valid marker for colon cancer. However, it has been reported that CEA is useful for detecting CRC (see Y. Kim, S. Lee, S. Park et al., "Gastrointestinal Tract Cancer Screening Using Fecal Carcinoembryonic Antigen," Ann. Clin. Lab. Sci., 2003; 33:32-38;

and R.S. Stubbs, D.M. Nadkarni and H.A. Monsey, "Fecal Carcinoembryonic Antigen in Colorectal Cancer Patients, Gut, 1986; 26:901-905). Copies of Kim et al. and Stubbs et al. will be submitted shortly.

Therefore, it is respectfully submitted that CEA is a valid marker for colon cancer detection.

Attention is directed to the top of page 4 of the enclosed April 23, 2009 KANAOKA DECLARATION, wherein the results for two markers other than COX-2 and CEA were tested, namely Ets-related transcriptional factor (E1AF) and C-myc. These two markers were previously reported to be involved in colon carcinogenesis as follows: E1AF: K. Nosho, M. Yoshida, H. Yamamoto et al., "Association of Ets-Related Transcriptional Factor E1AF Expression With Overexpression of Matrix Metalloproteinases, COX-2 and iNOS in the Early Stage of Colorectal Carcinogenesis," Carcinogenesis, 2005; 26:892-899); c-myc: S. Lagerholm, S. Dutta, P. Nair, "Non-invasive detection of c-myc p64, c-myc p67 and c-erbB-2 in colorectal cancer, Scand J. Gastroenterol, 2005;

40:1343-1350. Copies of Nosho et al. and Langerholm et al. will be submitted shortly.

The results for testing involving COX-2, E1AF and c-myc are shown at the top of page 4 of the enclosed April 23, 2009 KANAOKA DECLARATION as follows:

Comparison Among COX-2, E1AF and c-myc Assays

<u>marker</u>	<u>sensitivity</u>	<u>specificity</u>
COX-2	85.7% (60/70)	100.0% (34/34)
E1AF	27.5% (19/69)	96.7% (29/30)
c-myc	42.9% (15/35)	83.3% (20/24)

The above results show that the COX-2 assay had high sensitivity for detecting colorectal cancer, while maintaining high specificity compared with the other tested markers. None of the other tested markers had both high sensitivity and high specificity.

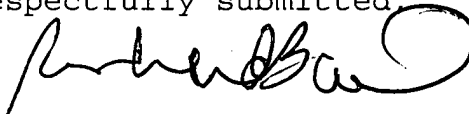
The applicant respectfully submits that the results shown in the April 23, 2009 KANAOKA DECLARATION are surprising and could not be expected from the disclosure of the cited references.

Withdrawal of each of the 35 USC 103 rejections is thus respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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RSB/ddf

Encs.: (1) PETITION FOR EXTENSION OF TIME
(2) DECLARATION UNDER 37 CFR 1.132 of
Shigeru KANAOKA dated April 23, 2009